Remarks

Favorable reconsideration of this application is respectfully requested. Claim 27 has been amended. No new matter has been added. Claims 15, 16 and 27 are pending.

Claims 15, 16, and 27 are rejected under 35 U.S.C. 103(a) as being unpatenable over Hidaka et al., (US 5,972,976) in view of Goodman and Gilman (1996), and Ragaz et al. (1997). Applicants respectfully traverse the rejection for at least the following reasons.

Claim 27 recites the following: The use of cisplatin in a method for treating at least one malignant tumor selected from the group consisting of blood cancer, leukemia, human colon adenocarcinoma, gastrointestinal cancer, lung cancer, breast cancer, and prostate cancer, which also uses the method comprising administering a therapeutically effective amount of at least one compound selected from the group consisting of (E)-4-[2-[2-[N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine, (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide, (E)-4-[2-[2-[N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide, (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine, (E)-4-[2-[2-[N-(2-hydroxyethyl)-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide, and (E)-4-[2-[2-[N-(2-hydroxyethyl)-N-[(p-methoxyphenyl)sulfonyl]-amino]phenyl]ethenyl]pyridine or a pharmaceutically acceptable salt thereof in combination with one other antitumor agent to the patient in need thereof, wherein the other antitumor agent is cisplatin, and the therapeutically effective amount of the at least one compound in combination with the other antitumor agent gives a synergistic inhibitory effect.

Applicants do not concede that carboplatin as the other antitumor agent does not exhibit similar effects with the claimed compounds as that of cisplatin.

The rejection states that one of ordinary skill in the art would have been motivated to combine a known anticancer drug employed in the treatment of breast cancer with the newly found drug that is capable of treating the same type of disease via a different mechanism in terms of a combination of Hidaka et al. with Goodman and Gilman, and

Ragaz et al.. The rejection also questions whether synergism is present rather than an additive effect.

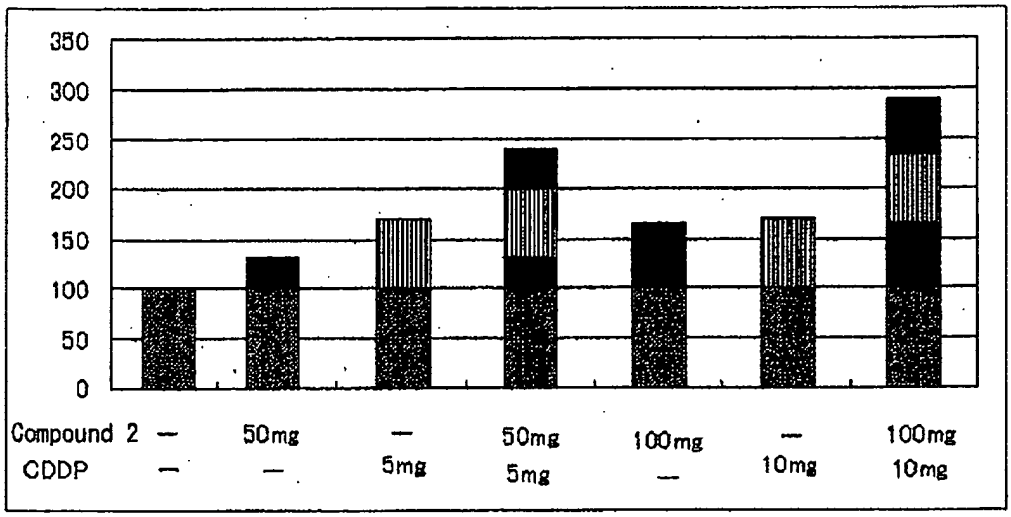
Applicants respectfully disagree with the conclusions made in the Office Action. For at least the reasons below, Applicants respectfully submit that their method provides unexpected results, and that one of skill in the art would not have an expectation of therapeutic synergism of a combination of each of the claimed six compounds with cisplatin, based on any combination of Hidaka et al., Goodman and Gilman, and Ragaz et al.

As recited by claim 27, the other antitumor agent used in the treatment method is "cisplatin", which Applicants have clearly demonstrated as having a synergistic inhibitory effect in combination with Compound 2 as seen in Table 1 of the present specification. Particularly, the T/C values of Table 1 exhibit a synergistic effect, not merely an additive effect, as discussed below.

T/C value is an indicator that shows how long survival times of animals of a treated group are extended compared to those of a control group. More precisely, a T/C value is calculated as follows: T/C = (a median survival time (MST) of a treated group/MST of a control group) x 100.

For example, in case that a MST of a treated group is 11 days and a MST of a control group is 10 days, T/C = 11/10 x 100 = 110 (%). In other words, the survival advantage from drug administration is 10%. As shown in Table 1, the T/C value in administering only Compound 2 ((E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)-sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide; 50 mg) is 130%, and this means a survival advantage is 30%. The T/C value in administering only CDDP (5 mg) is 170%, and that means a survival advantage is 70%.

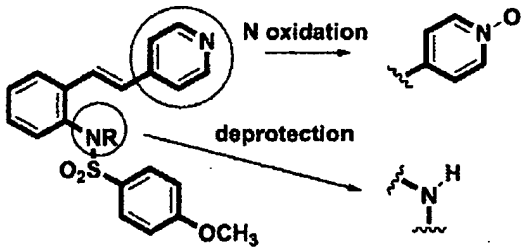
The graph below shows T/C values compiled from the original results reported in Table 1 of the present specification of record. The graph shows T/C values of a single administration of Compound 2 (at 50 mg and at 100 mg) and a single administration of CDDP (at 5 mg and at 10 mg), and shows a combined administration of Compound 2 (50 mg) with CDDP (5 mg), and a combined administration of Compound 2 (100 mg) with CDDP (10 mg).



A sum of each survival advantage obtained in each single administration of two drugs may be considered to show an expected survival advantage of a combined administration of the two drugs, i.e. an additive effect. Meanwhile, a survival advantage is considered to be synergistic, not additive, when a survival advantage value obtained in a combined administration of two drugs is larger than a sum of each survival advantage value obtained in each single administration of the two drugs. Applicants have clearly shown a synergistic effect based on their original disclosure.

As shown above, if the single administrations of Compound 2 (at 50 mg) and CDDP (at 5 mg) are combined (i.e. additive result), the expected survival advantage would be 100% (30% for Compound 2 + 70% for CDDP). However, as shown in Table 1 and the above graph, the actual T/C value in a combined administration of the two drugs is 240%. This means the survival advantage of the combined administration is 140%. The survival advantage (140%) is clearly larger than the expected value (100%), and hence, the advantage is synergistic, rather than additive. Similarly, the survival advantage of a combined administration of Compound 2 (100 mg) with CDDP (10 mg) is 190%, which is larger than the expected value 135% (65% for Compound 2 + 70% for CDDP). Thus, Applicants have shown that combined administration as claimed has an advantageous, synergistic effect that goes well beyond an additive effect. The references cited, however, neither provide a suggestion, nor any expectation of success for one of skill in the art to arrive at the benefits of the invention of claim 27.

Regarding the other compounds of claim 27, Applicants also respectfully submit that along with Compound 2 ((E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide), one of skill in the art would reasonably expect, based on Applicants' teachings, that the other five claimed compounds would show a synergistic inhibitory effect when combined with cisplatin for administration to a patient. The rejection states that how the compounds are metabolized *in vivo* is irrelevant. Applicants respectfully disagree based on the submitted evidence below. In particular, Applicants respectfully submit that one of skill in the art would clearly recognize that, among the other five claimed compounds, Compound 3 ((E)-4-[2-[2-[N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide) can be metabolized in a living body, and converted to an active form. Compound 3, which finds support as an active antitumor agent in U.S. 5,972,976, also is known to metabolize as follows. The pyridine moiety is converted to pyridine N-oxide group and the substituent (R) attached to the nitrogen of the sulfonamide moiety is eliminated and converted to an NH group, and hence, converted to an active form:



Applicants respectfully submit Appendix 1, attached herewith, which shows graphs demonstrating comparative metabolic results of Compound 3 (designated as HMN-176) against Compounds 1, 2, 5, and 6. As shown in Appendix 1, it is clear that Compound 2, along with compounds 1, 5, and 6 also convert into an active form, i.e. Compound 3 (HMN-176) and would therefore behave similarly as compound 3. As to Compound 4 ((E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]-ethenyl]pyridine), it is clear that Compound 4 also would convert into Compound 3 as seen from the data reported in graphs (1) and (2) of Appendix 1. In other words, the N-acetyl group of Compound 4 would be expected to convert to an NH group in view of the

data in graph (2), and the pyridine moiety would be expected to convert to pyridine N-oxide group in view of the data in graph (1).

Thus, Compounds 2 and 3 as well as the other four claimed Compounds 1, 4, 5, and 6 would be expected to convert to an active form in a living body. Accordingly, one would expect that each of the claimed six compounds would exhibit synergism when administered with cisplatin, based on Applicants' original disclosure and experimental data for Compound 2, and the comparative metabolic results of Appendix 1.

Accordingly, it is clear that a combined administration with cisplatin would be expected to show a synergistic effect for all the claimed six compounds in claim 27, and those skilled in the art would not have arrived at the advantageous effects of claim 27 based on Hidaka et al., Goodman and Gilman, Ragaz et al. Consequently, claim 27 and its dependent claims 15 and 16 are patentable over Hidaka et al., Goodman and Gilman, and Ragaz et al. Favorable reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above amendments and remarks, Applicants respectfully request favorable reconsideration of this application in the form of a Notice of Allowance. If any questions arise regarding this communication, the Examiner is invited to contact Applicants' representative listed below.

Respectfully submitted,

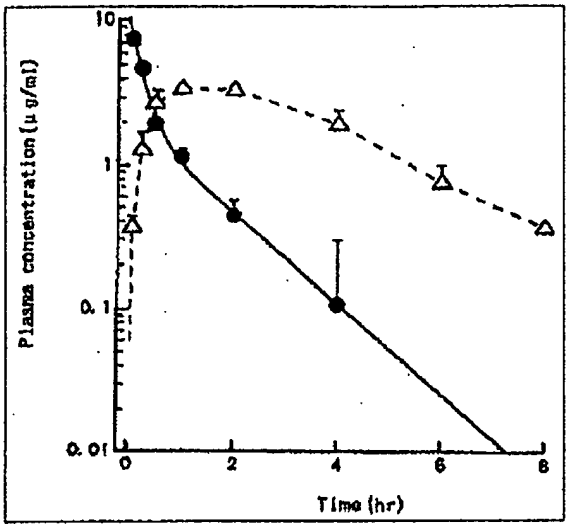
HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. Box 2902
Minneapolis, MN 55402-0902
(612) 455-3800

Dated: July 27, 2009

By: _____
Douglas P. Mueller
Reg. No. 30,300
DPM/baw

APPENDIX 1

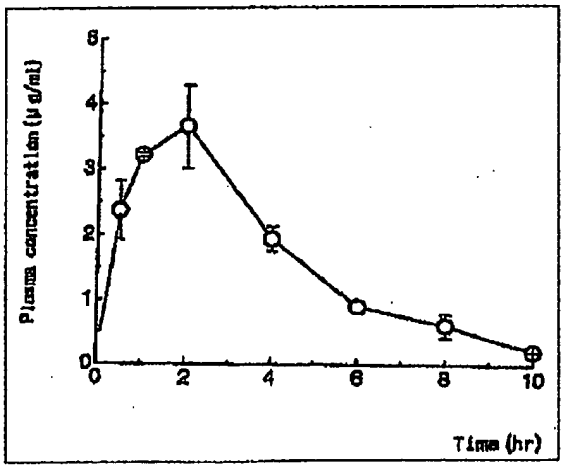
(1) Transition of plasma concentrations of HMN-154 (Compound 1: ●), and HMN-176 (Compound 3: △) after intravenous administration of 10 mg/kg HMN-154.



HMN-154: (E)-4-[2-[2-[N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine

HMN-176 : (E)-4-[2-[2-[N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide

(2) Transition of plasma concentrations of HMN-214 (Compound 2: ●), and HMN-176 (○) after oral administration of 20 mg/kg HMN-214 to mice.

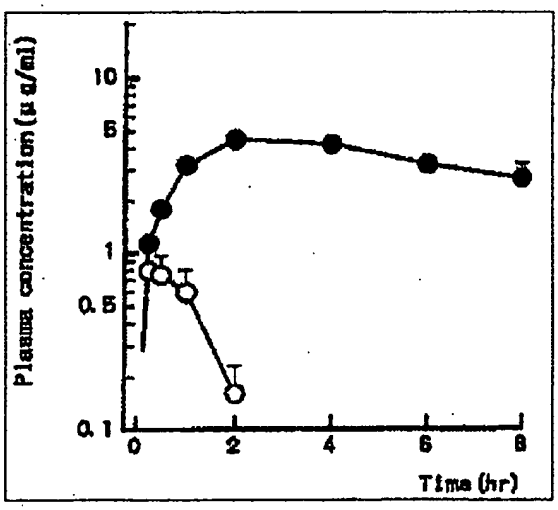


HMN-214: (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide

HMN-176: (E)-4-[2-[2-[N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide

HMN-214 was not observed in order to be metabolized into HMN-176 immediately.

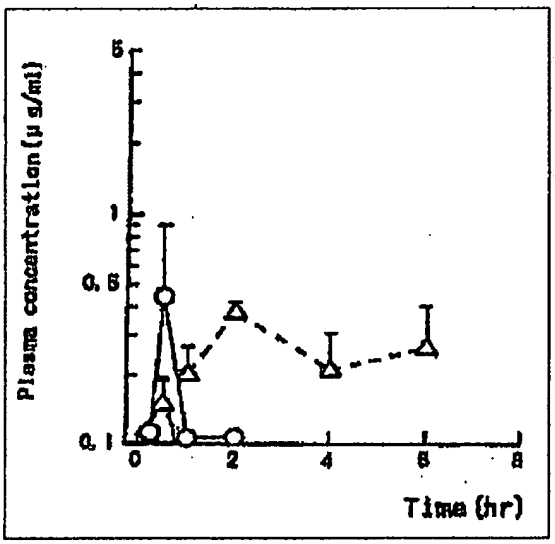
(3) Transition of plasma concentrations of HMN-206 (Compound 5; ●), and HMN-176 (○) after oral administration of 30 mg/kg HMN-206 to mice.



HMN-206: (E)-4-[2-[2-[N-(2-hydroxyethyl)-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide

HMN-176: (E)-4-[2-[2-[N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide

(4) Transition of plasma concentrations of HMN-191 (Compound 6; ○), and HMN-176 (△) after oral administration of 30 mg/kg HMN-191 to rats.



HMN-191: (E)-4-[2-[2-[N-(2-hydroxyethyl)-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine

HMN-176: (E)-4-[2-[2-[N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide